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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FISH & RICHARDSON PC			EXAMINER	
P.O. BOX 1022			ZARA, JANE J	
MINNEAPOLIS, MN 55440-1022			ART UNIT	PAPER NUMBER
			1635	
DATE MAILED: 03/02/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary**Application No.**

10/074,694

Applicant(s)

KAHN ET AL.

Examiner

Jane Zara

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 April 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-37 is/are pending in the application.
- 4a) Of the above claim(s) 4-16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2,3 and 17-37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>4-05</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office action is in response to the communication filed 4-5-05.

Claims 2-37 are pending in the instant application.

Election/Restrictions

This application contains claims 4-16, drawn to an invention nonelected with traverse in the response filed 7-26-04. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to Arguments/Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 2, 3 and 17-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action mailed 10-6-04 and for the reasons set forth below.

Applicant's arguments filed 4-5-05 have been fully considered but they are not persuasive. Applicant argues that the instantly claimed invention is adequately described as set forth in the specification, and as relying upon the 1988 disclosure of Steeg et al and upon the 1991 disclosure by Stahl et al. Applicant also argues that the

specific structures of the broad genera claimed are provided by the sequence identification numbers of nm23H1 and nm23H2, in combination with the limitation of the recited nm23 biological activities, comprising Rad binding, promoting a Rad activity, nucleotide diphosphokinase activity, and inhibiting Rad-nm23 binding. The claims are drawn to methods of modulating Rad activity in a cell comprising the administration of a polypeptide that comprises at least 60% sequence identity with the coding region of SEQ ID NO: 3 or 5, or a fragment thereof of at least 5 amino acids in length.

Contrary to Applicant's assertions, the broad genera encompassed by polypeptides with at least 60-98% sequence identity with the coding region of SEQ ID NO: 3 or 5, or fragments thereof with at least 5 amino acids in length, and comprising nm23 biological activity, are not adequately described. The specification teaches mouse and human polynucleotide sequences (SEQ ID NOs: 3 and 5) encoding Rad GAP (ras related protein associated with diabetes or nm23), as well as providing sequence comparisons to Ras. Stahl et al (Cancer Res., Vol. 31, pages 445-449, 1991) teaches the cloning and characterization of expression of nm23-H2. Steeg et al (J.N.C.I., Vol. 80, No. 3, pages 200-204, 1988) teaches the polynucleotide sequence and characterization of expression of nm23-1.

The teachings of the prior art and of the instant disclosure do not provide adequate description of the broad genera encompassed by polypeptides with at least 60% identity with SEQ ID Nos: 3 and 5 which comprise one or more activities, including Rad binding, promoting a Rad activity, nucleotide diphosphokinase activity, and/or inhibiting Rad-nm23 binding. The specification and prior art do not provide adequate

description of fragments of at least 5 amino acids that comprise one or more activities of Rad binding, promoting a Rad activity, nucleotide diphosphokinase activity, and/or inhibiting Rad-nm23 binding. It is unclear what structural features, motifs, domains and variations thereof are minimally required for the various activities claimed. The genera claimed encompass a myriad of species (e.g. thousands of sequences) and the specification fails to provide a representative number of species for such broadly claimed genera. Concise features that could distinguish members within the genera from others are missing from the disclosure and the art. And because the genera are highly variant, the description provided is insufficient. For these reasons, the rejection for lacking adequate written description is maintained.

Claims 2, 3, 17-37 are rejected under 35 U.S.C. 112, first paragraph, for lacking enablement over the scope claimed for the reasons of record set forth in the Office action mailed 10-6-04 and for the reasons set forth below.

Applicant's arguments filed 4-5-05 have been fully considered but they are not persuasive. Applicant argues that one of skill in the art would have been well aware of a number of methods, in addition to those discussed in the enablement rejection of 10-6-04, to deliver a polypeptide to a cell in vivo. Applicant also argues that liposomal delivery systems were known and in development at the time of filing, citing several review articles regarding liposomal protein delivery. Applicant is correct that liposomes are well known in the art for enhancing the delivery of various molecules to target cells. But, contrary to Applicant's assertions, the ability to deliver adequate quantities of a

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polypeptide to a target cell in vivo, and further whereby a biological response is obtained, is not a predictable endeavor. And, contrary to Applicant's assertions, the successful delivery of a polypeptide to a target cell in vitro is not representative or correlative of the ability to do so in vivo. The conditions obtained in a test tube or a culture dish are not necessarily reproduced or reproducible in vivo. A cell in vitro, for instance, can be exposed to culture conditions containing very high concentrations of a polypeptide for cellular delivery. The ability to achieve delivery in vivo requires undue experimentation. One cannot extrapolate from in vitro success to in vivo success for the delivery of a polypeptide - and further whereby Rad activity is modulated in that target cell in vivo. And one cannot extrapolate from the in vivo success - for obtaining adequate delivery and efficacy of one polypeptide - to the in vivo success of a different polypeptide. This must be determined empirically. It is highly unpredictable.

Applicants have not provided adequate guidance in the specification toward a method of modulating Rad activity in a cell in vivo comprising the administration of an nm23 polypeptide, a fragment of nm23 polypeptide or a homolog of nm23 polypeptide to the cell, or comprising the administration of an nm23H1 or nm23H2 polypeptide to the cell. The specification very generally discusses co-precipitation experiments indicating a relationship between Rad and nm23 and in promoting GTP hydrolysis. These in vitro experiment are not correlative or representative of the ability to successfully deliver adequate quantities of a representative number of species of the broad genera claimed, whereby Rad binding, Rad activity and/or diphosphokinase activity is modulated, or

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whereby Rad and nm23 binding is inhibited. For these reasons, the rejection for lacking enablement over the scope claimed is maintained.

New Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 2, 3, 17-31 and 37 are rejected under 35 U.S.C. 102(e) as being anticipated by Bandman et al.

Bandman et al (USPN 6,087,125) teach methods of modulating Rad activity in a cell in vitro comprising the administration of a polypeptide comprising at least 60% sequence identity with SEQ ID NO: 5, or comprising the administration of a fragment of at least 5 amino acids thereof (See the accompanying sequence alignment data between SEQ ID NO: 5 of the instant application and SEQ ID NO: 5 of USPN 6,087,125; see also col. 1-2; col. 15 and claim 2).

Claims 2, 3, 17-37 are rejected under 35 U.S.C. 102(e) as being anticipated by King et al.

King et al (USPN 6,329,198) teach methods of modulating Rad activity in a cell in vitro comprising the administration of a polypeptide comprising at least 60% sequence identity with SEQ ID NO: 3 or 5, or comprising the administration of a fragment of at least 5 amino acids thereof, or comprising the administration of a polypeptide differing in amino acid sequence up to 10 residues in SEQ ID NO: 3 or 5 (See the accompanying sequence alignment data between SEQ ID NOs: 3 and 5 of the instant application and SEQ ID NOs: 1 and 5 of USPN 6,329,198; see also col. 1-2, 4-5, 8-9 and claims 1-4).

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765**. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose

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telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
2-24-06

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JANE ZARA, PH.D.
PRIMARY EXAMINER